What Should the Serum Creatinine Be After Transplantation? An Approach to Integrate Donor and Recipient Information to Assess Posttransplant Kidney Function

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Abstract: BACKGROUND Knowledge of an optimal expected serum creatinine (SCr) would be useful to detect early renal dysfunction after transplantation. Current measurements of posttransplant function rely on the recipient's SCr and calculations of estimated glomerular filtration rate (eGFR), based on recipient age, weight, and sex. Renal function after transplantation, however, also depends on the donor supply of functioning nephrons and adaptation in GFR of a single kidney. METHODS We developed a formula to predict the optimal expected SCr after transplantation derived from donor and recipient Cockroft-Gault GFRs and adjusted for the single kidney adaptive response. We compared the expected SCr with the lowest observed SCr in a cohort of living (79) and deceased (67) donor allograft recipients followed up over 5 years. RESULTS Expected SCr correlated with the observed SCr in both living and deceased donor kidney recipients, correlation was stronger among living donor kidney recipients. Recipient-to-donor body weight ratio was significantly associated with the difference between expected and observed SCr, suggesting that recipient body weight is a major predictor of posttransplant renal function. The difference between expected and observed SCr was significantly greater among deceased donor kidney recipients, suggesting poorer function in these patients, which was not detected by SCr or estimated GFR alone. CONCLUSIONS Calculation of expected renal function for a given donor-recipient combination adds relevant information to assessment of allograft function. Future studies will permit determination of a threshold difference between expected and observed SCr that should trigger investigation and potential intervention to improve allograft function.

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Background. Knowledge of an optimal expected serum creatinine (SCr) would be useful to detect early renal dysfunction after transplantation. Current measurements of posttransplant function rely on the recipient's SCr and calculations of estimated glomerular filtration rate (eGFR), based on recipient age, weight, and sex. Renal function after transplantation, however, also depends on the donor supply of functioning nephrons and adaptation in GFR of a single kidney. **Methods.** We developed a formula to predict the optimal expected SCr after transplantation derived from donor and recipient Cockroft-Gault GFRs and adjusted for the single kidney adaptive response. We compared the expected SCr with the lowest observed SCr in a cohort of living (79) and deceased (67) donor allograft recipients followed up over 5 years. **Results.** Expected SCr correlated with the observed SCr in both living and deceased donor kidney recipients, correlation was stronger among living donor kidney recipients. Recipient-to-donor body weight ratio was significantly associated with the difference between expected and observed SCr, suggesting that recipient body weight is a major predictor of posttransplant renal function. The difference between expected and observed SCr was significantly greater among deceased donor kidney recipients, suggesting poorer function in these patients, which was not detected by SCr or estimated GFR alone. **Conclusions.** Calculation of expected renal function for a given donor-recipient combination adds relevant information to assessment of allograft function. Future studies will permit determination of a threshold difference between expected and observed SCr that should trigger investigation and potential intervention to improve allograft function.

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Antigen-independent factors, such as donor age, relative donor and recipient sizes, donor cause of death, kidney mass, donor glomerular filtration rate (GFR), recipient age, and obesity are all associated with graft and patient survivals after transplantation.[1-10] These factors are likely to impact renal function well before the endpoint of graft failure, but detection of early allograft dysfunction is challenging, as the true "baseline", that is, optimal renal function for a given donor-recipient combination, is not known. The lowest observed creatinine (LoObsSCr) is often presumed to reflect baseline renal function, but whether this is a true baseline or reflects some ongoing renal dysfunction is not known.

Renal function is largely determined by the body's metabolic demand.[11-16] Thus, GFR is highly correlated with metabolic rate, and its key variables weight, age, and sex are incorporated into formulae to estimate GFR (eGFR).[17-19] Interestingly, these variables also correlate with nephron number and kidney size.[11,13,14,20] Allograft function is generally assessed by measuring the recipient's serum creatinine (SCr) and using eGFR calculations, derived in subjects with native kidneys, which incorporate the recipient's age, sex, and weight.[17,18,21,22] Posttransplant renal function is determined by both the metabolic demand of the recipient and the nephron supply of the donor, but donor factors are rarely taken into account.[2,6,12,23] In addition, GFR of a single kidney must respond to an increase in metabolic demand.[16,24,25] This adaptive increase in GFR (AI-GFR), although never a true

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doubling, is predictable in healthy living donors (LDs).[12,26] In the setting of transplantation, this AI-GFR is likely less predictable given additional nephron loss associated with periprocedural and immunologic renal injury and nephrotoxic medication use. Given these peculiarities of transplantation, how best to determine whether a given recipient's renal function is "good enough" or could/should be better is an important clinical challenge.

Two groups have proposed calculations to predict expected posttransplant kidney function by incorporating both donor and recipient information.[27,28] Sberro et al[28] derived a formula from recipient and donor Cockcroft and Gault GFRs (CG-GFR) to calculate a "best possible" SCr in renal allograft recipients. Oh et al[27] derived an "ideal" creatinine prediction formula by regression of observed SCr plotted against the renal allograft weight-recipient body surface area ratio. Both studies included only LD transplants, therefore generalizability to deceased donor (DD) recipients, which may be the greater group of concern, was not addressed. In addition, although clinical variables included in the Sberro formula are readily available, they did not consider the AI-GFR of a single kidney in their formula and therefore may be subject to a biased overestimation of expected GFR. The Oh formula requires allograft weight which is not routinely collected, limiting its utility. Nonetheless, these papers suggest that establishment of an "ideal" SCr for an individual donor-recipient combination would prompt therapeutic intervention when observed function differed significantly from expected function.[27,28]

In this proof-of-principle study, we have developed an adapted formula to calculate the posttransplant expected SCr (ExpSCr), by integrating parameters reflecting donor supply, recipient demand, and the physiology of the single kidney's adaptive increase. Given that there is no way to know what a given donor-recipient SCr should be, we retrospectively evaluated the performance of the ExpSCr compared to the observed creatinines (ObsScr) in recipients of both LD and DD kidneys over 5 years.

METHODS

Patient Groups

Kidney function predonation and postdonation was analyzed in a group of 27 consecutive LDs. Expected and observed SCr were analyzed in 146 consecutive recipients of 67 DD and 79 LD kidneys. All patients were transplanted at the University of Alberta Hospital and followed for a mean (± SD) of 5.7 ± 1.4 years. Both transplant groups received similar immunosuppressive therapy, based on steroids, mycophenolate mofetil, and tacrolimus. Delayed graft function was defined as the requirement for dialysis within the first week after transplantation. The study was approved by the Human Research Ethics Board of the University of Alberta.

Donor and Recipient Data and Renal Function Measurements

Baseline data were collected from donors and recipients at the time of donation and transplantation. All body weights used for the derived formulas are based on measured total body weights, as baseline for the recipient, the weight on the first outpatient visit was used. Kidney function was measured by SCr and by creatinine-based eGFR using the CG, Modification of Diet in Renal Disease and CKD-EPI formulas.[17-19,29] In recipients, posttransplant SCr was measured daily until day 7 and then 6 monthly. There was no loss-to-follow up. The LoObsSCr was obtained for each patient as the lowest SCr measured within the first posttransplant year.

Development of the Equation to Calculate the Expected Posttransplant SCr

Assessment of AI-GFR: the eGFR of 27 consecutive LDs were analyzed before and after donation to quantify the physiologic AI-GFR after removal of the contralateral kidney for transplantation. The LD_GFR_pre and LD_GFR_post were estimated from the LoObsSCr 1 year before and 1 year after donation using the CG formula. The linear relationship between LD_GFR_pre and LD_GFR_post was tested by Pearson product-moment correlation. Linear regression analysis was used to develop an equation to predict LD_GFR_post based on LD_GFR_pre (a = regression coefficient and b = intercept):

$$LD\_GFR\_post = a^{*} D\_GFR\_pre + b \qquad 1$$

Integration of recipient demand and donor supply in a creatinine-based formula: demand and supply are largely defined by the key metabolic variables age, weight, and sex. We used the CG formula which captures all 3 of these metabolic markers.[17] Incorporation of body weight was considered important because mismatch between donor and recipient weight is a recognized predictor of long-term graft function[6]:

$$CG\_GFR\,[ml/\min] = \frac{age \times bwt \times gender}{SCr} \qquad 2$$

Clinically, SCr is most often used; therefore, the formula was solved accordingly:

$$SCr\,[\mu mol/L] = \frac{age \times bwt \times sex}{GFR} \qquad 3$$

Posttransplant kidney function is determined by the ratio of recipient (R) demand to donor (D) supply. As used by Sberro et al,[28] the above formula is expressed as follows:

$$R\_ExpSCr\,[\mu mol/L] = \frac{R\_age \times R\_bwt \times R\_sex}{D\_GFR\_post} \qquad 4$$

Considering the AI-GFR in a single kidney this formula can be extended as follows incorporating formula (1) above:

$$R\_ExpSCr\,[\mu mol/l] = \frac{R\_age \times R\_bwt \times R\_gender}{a^{*}D\_GFR\_pre + b} \qquad 5$$

Here, the numerator reflects the recipient's demand and the denominator reflects the donor supply and the donor's expected AI-GFR. This is better illustrated by transforming the previous formula as:

$$R\_ExpSCr\,[\mu mol/L] = \frac{R\_age \times R\_bwt \times R\_gender}{a^{*}\left(\frac{D\_age \times D\_bwt \times D\_gender}{D\_SCr}\right) + b} \qquad 6$$

Statistical Methods

Descriptive statistics were used for the analysis of study groups, Kaplan-Meier survival estimates and log-rank tests were used for comparison of survival curves. Mean values

and frequencies were compared using the Wilcoxon test and the Fisher exact test, respectively. To characterize and quantify the relationship between parameters, Pearson correlation coefficients were calculated, and linear regression analyses were performed as a first step. In addition, Bland-Altman plots were generated for better visualization of the data and better assessment of concordance between ExpSCr and LoObsSCr. Bias (mean difference between ExpSCr and LoObsSCr) and limits of agreement (1.96 × standard deviation of the differences) with their 95% confidence intervals were determined.[30,31] Statistics were computed using the SAS version 9.2 (SAS Institute Inc., Cary, NC).

RESULTS

Donor and recipient demographics were not different between LDs and DDs, as shown in Table 1. Predonation eGFR, estimated by 3 formulae, was higher among DDs ($P < 0.05$). Recipients in both groups were similar in age, weight, and sex distribution. The DD recipients had longer ischemia times, more HLA mismatches, and more delayed graft function. Mean follow-up was 5.7 ± 1.4 years. Six (7.6%) LD and 13 (19.4%) DD recipients died. All DD recipient deaths occurred with functioning grafts, 1 LD recipient experienced graft failure due to nonadherence before death. One patient returned to permanent dialysis in each group. Five-year graft and patient survival rates were 94% and 94%, respectively, for LD and 83% and 84 %, respectively, for DD recipients.

Adaptive Increase in Living Donor Kidney Function Post-donation

The AI-GFR after donation was assessed by comparing predonation (LD_GFR_pre) and postdonation (LD_GFR_post) eGFRs in 27 LDs. The LD_GFR_pre and LD_GFR_ postcorrelated strongly (r = 0.89, $P < 0.0001$) with a mean AI-GFR of 36 ± 18% (Figure 1A). Linear regression demonstrated a high predictive accuracy (Figure 1B). The resulting equation to predict LD_GFR_post from LD_GFR_pre is as follows:

$$LD\_GFR\_post = 0.6 * LD\_GFR\_pre + 8.7 \qquad 7$$

The derived formula for ExpSCr (see *Methods*) can therefore be calculated as follows:

$$ExpSCr\,[\mu mol/l] = \frac{R\_age \times R\_bwt \times R\_gender}{0.6 * \left(\frac{D\_age \times D\_bwt \times D\_gender}{D\_SCr}\right) + 8.7} \qquad 8$$

Formula parameters are: age = (140 – age) in years, bwt = body weight in kilograms, and sex = 1.23 for men and 1.04 for women.

Performance of ExpSCr Equation in Living and Deceased Donors

Agreement Between Observed and Expected SCr

The LoObsSCr and the ExpSCr showed a moderate but significant correlation during the first posttransplant year that was higher in LD compared to DD recipients (r = 0.64 vs 0.36, $P < 0.001$ vs 0.003, respectively). Data are displayed using Bland-Altman plots (Figure 2). The limits of agreement were smaller in LD (–47.3 μmol/L to 72.0 μmol/L) compared to DD (–87.0 μmol/L to 70.6 μmol/L) recipients implying a stronger concordance in LD recipients. Of interest, the outlier within the LD recipients with the highest disagreement (ExpSCr of 83 μmol/L vs LoObsScr of 170 μmol/L) had ischemia of two thirds of the donor kidney due to vascular problems identified in a posttransplant perfusion scan. The

TABLE 1.

Donor and recipient demographics

	Living donors (n = 79)	Deceased donors (n = 67)	*P*
Age, y	44 ± 11	42 ± 17	0.55
Sex (M/F)	26/53	30/37	0.14
Weight, kg	75 ± 14	78 ± 20	0.35
SCr at donation, μmol/L	72 ± 13	68 ± 26	0.25
CG eGFR, mL/min	113 ± 30	138 ± 66	0.005
MDRD eGFR, mL/min	89 ± 28	114 ± 61	0.0015
CKD-EPI eGFR, mL/min	95 ± 20	105 ± 29	0.015
	Living donor recipients (n = 79)	**Deceased donor recipients (n = 67)**	
Age, y	48 ± 15	52 ± 13	0.071
Sex (M/F)	56/23	42/25	0.39
Weight, kg	82 ± 21	79 ± 17	0.38
Cold ischemia time, min	202 ± 96	980 ± 342	0.0001
Revascularization time, min	36 ± 7	40 ± 8	0.0041
DGF	1	13	
HLA mismatches	3 ± 2	5 ± 1	0.0001
Duration of follow-up[47]	2202 ± 456	2056 ± 562	0.038
Lost follow-up	0	0	
Death	6	13	
Death with functioning graft	5	13	
Failed grafts	1	1	

MDRD, Modification of Diet in Renal Disease.

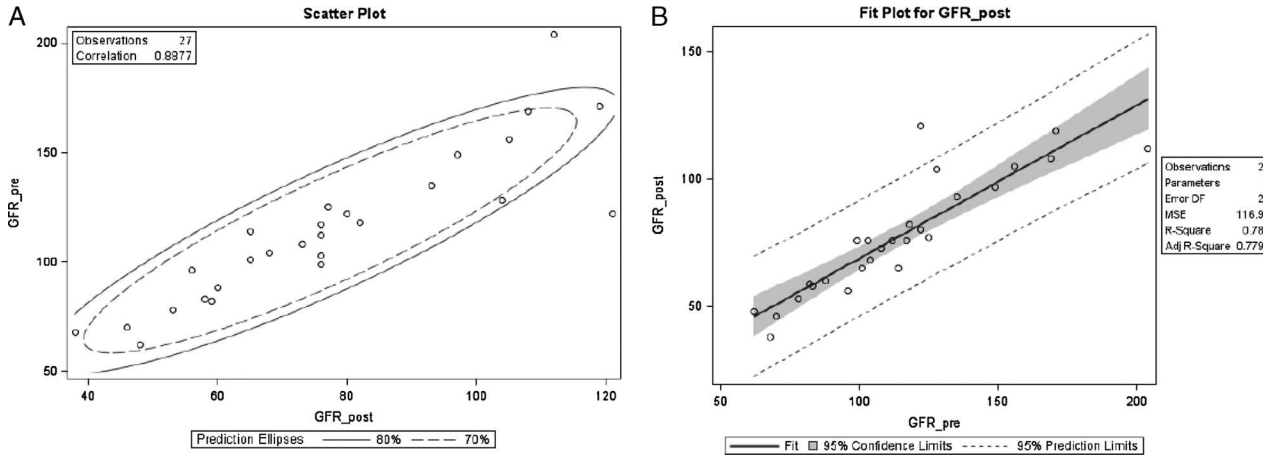

FIGURE 1. Correlation between pre- and post-donation kidney function. A, The scatter plot shows the CG GFR level before and after donation for 27 living donors (r = 0.89, $P < 0.0001$). B, The fit plot gives the 95% confidence interval and prediction limits of the linear regression model (F = 92.91, $P < 0.0001$).

bias for recipients of LD and DD allografts was 12.3 μmol/L and −8.2 μmol/L, respectively, indicating that the calculated ExpSCr slightly overestimates the actual measured LoObsSCr in LD and vice versa in DD recipients.

Impact of Body Weight Ratio on Transplant Function

In Figure 3, the difference between ExpSCr and LoObsSCr is plotted against recipient to donor (R/D) body weight ratio. The scatter plots show that extremes of R/D body weight ratio are associated with widening differences between ExpSCr and LoObsSCr. Correlation between transplant function and R/D body weight ratio was highly significant among LD recipients (Figure 3A; r = 0.62, $P = 0.000$), but less strong among DD recipients (Figure 3B, r = 0.34, $P = 0.006$). Similar analyses of R/D age or sex differences showed no correlation (data not shown).

Five-Year Follow-up of Transplant Function

Table 2 gives for defined time points the ObsScr values, estimated CG-GFR levels and differences between ExpSCr and ObsSCr for the LD versus DD recipients over 5 years. At day 7, renal function was significantly better in LD compared to DD kidneys. However, from month 3, SCr and CG-GFR were not significantly different between LD and DD recipients (eGFR by Modification of Diet in Renal Disease or CKD-EPI formulae were also not different, data not shown). In contrast, the difference between ExpSCr and ObsSCr was consistently more negative (i.e., ObsScr was higher than expected) among DD compared to LD recipients, suggesting persistently better transplant function in LD compared to DD recipients. From year 1 onward, the observed SCr was on average 40% higher than expected in DD recipients compared to 10% higher in recipient of LD kidneys ($P < 0.05$, Table 2).

DISCUSSION

Calculation of expected compared to observed SCr adds information to assessment of renal transplant function. Comparison of ExpSCr versus ObsSCr over the first 5 years showed that whereas standard measurements only detected a difference in renal function early after transplantation, the integrated formula identified a persistently larger gap between expected and achieved function in DD compared to LD recipients. This observation is plausible and likely reflects the multitude of factors negatively impacting DD kidneys and the well-recognized better graft and patient survival in LD recipients.[32-34]

Given that there is no method to determine the optimal SCr for a given donor-recipient combination, the closest approximation must logically incorporate data reflecting donor nephron supply, recipient metabolic demand, and adjustment for the expected physiological AI-GFR in a single kidney.[11-15] The observations in our LD cohort corroborate the previously reported AI-GFR in the remaining donor kidney of around 30% to 40%.[24-26,28] The AI-GFR in the single transplanted kidney has not been well described, therefore we have modified Sberro's approach using the AI-GFR derived from living donors.[28] The AI-GFR in a renal allograft is likely to be lower than that in a native single kidney and may be lower in DD than LD kidneys. The impact of donor age on the AI-GFR is difficult to predict; however, a recent publication suggests that the compensatory response of the remaining kidney in older donors is similar to standard donors.[35] Application of the LD AI-GFR here therefore represents a "best-case" scenario.

Posttransplant LoObsSCr correlated significantly with ExpSCr in recipients of both LD and DD kidneys. In addition, the Bland-Altman plot showed a better agreement of LoObsSCr and ExpSCr in recipients of LD compared to DD kidneys. The weaker concordance in DD recipients does demonstrate some internal consistency and likely reflects greater heterogeneity among DDs. Importantly, terminal SCr in DDs may not accurately reflect the donor's true baseline as SCr may be impacted by volume resuscitation or acute kidney injury predonation. As shown in Table 1, donor age, sex, body weight, and SCr were not different between LD and DD, although eGFRs were higher among DDs. How imprecise individual predonation SCr levels would bias formula accuracy, and in which direction, is difficult to predict. On average, SCr was 6% lower among DDs, despite similar anthropomorphic data to LDs, suggesting this error may be small. The real value of determining discrepancies between expected and observed SCr after transplantation is to allow for the identification of outliers, that is, posttransplant creatinine values that are significantly higher than expected should

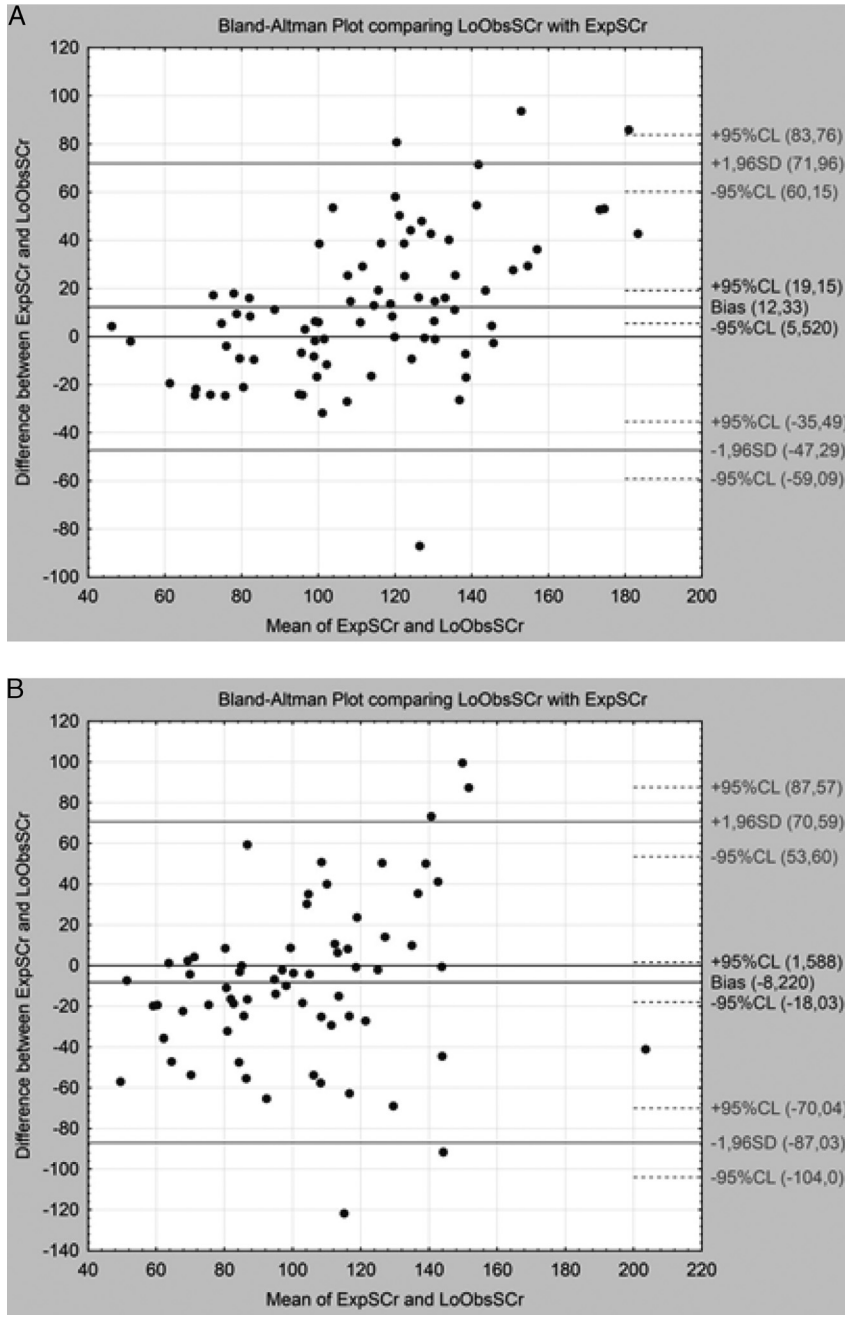

FIGURE 2. Bland-Altman plots comparing lowest observed and expected serum creatinine in the first year posttransplant in recipients of living and deceased donor kidneys. The Bland-Altman plots show the difference between LoObsSCr and ExpSCr against their mean during the first posttransplant year in 79 recipients of living donor (A) and 67 recipients of deceased donor kidneys (B). Bias—mean difference between LoObsSCr and ExpSCr; limits of agreement—1.96 × standard deviation of the differences with 95% confidence intervals.

prompt thought and investigation. Clinically, erring on the side of a lower ExpSCr would be preferable to overestimation of ExpSCr, as in the latter case, a poorly functioning kidney may not be identified early enough for successful intervention. Conversely, however, potential anxiety relating to investigation of overdiagnosed renal dysfunction is also important. Given the lack of a gold standard, prospective follow-up of the differences between ExpSCr and ObsSCr, correlated with clinical outcomes over time, will best permit determination of a clinically relevant threshold for this difference, not possible in this cohort given the small numbers and short follow-up.

Body weight was a key factor impacting differences between expected and observed function. The R/D weight ratio correlated significantly with the difference in ExpSCr versus LoObsScr in both LD and DD recipients. A potential source of confounding is that recipient and donor weights, respectively, appear on the numerator and denominator of the ExpSCr formula (formula 6). Age and sex ratios, appearing in similar positions in the formula, were not correlated however, arguing for a true impact of body weight on renal function. The lack of significant impact of R/D ratios of sex or age compared to body weight on the AI-GFR after transplantation is likely due to the

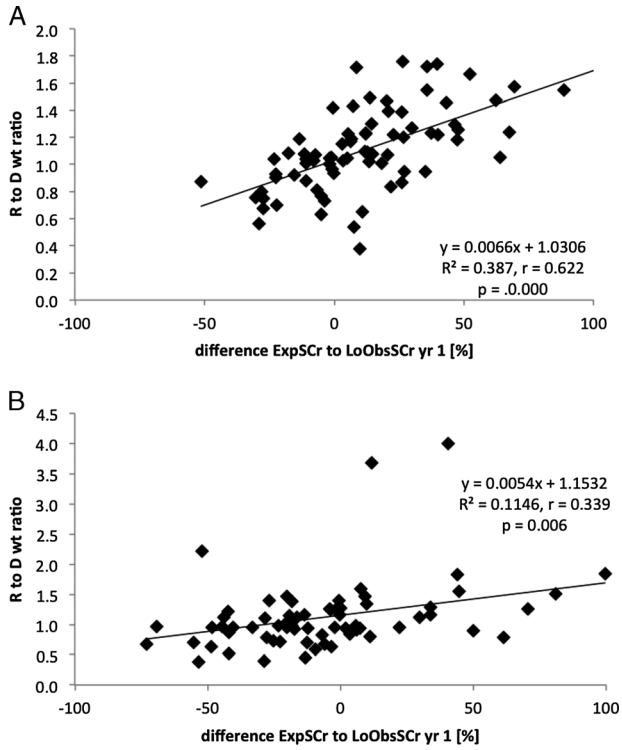

FIGURE 3. Relationship between the difference in expected to observed serum creatinine and the ratio of recipient to donor body weight. The scatter plots indicate the correlation between the difference in ExpSCr to LoObsSCr in 79 recipients of living donor kidneys (A), LD recipients and in 67 recipients of deceased donor kidneys (B), DD recipients, respectively. The difference between ExpSCr and LoObsSCr is given in percent on the x-axis, negative values denote a transplant function lower, positive values higher than expected.

overriding effect of weight as key determinant of metabolic demand.[16,36,37]

In addition, if the correlation between R/D weight ratio and the difference in ExpSCr versus LoObsScr was an artifact of calculation, the relationships should have been more similar between LDs and DDs. Although seemingly counterintuitive, given that a high R/D weight ratio is a risk factor for poorer long-term graft function, our data suggest that in the first 5 years, the AI-GFR is higher than anticipated for small kidneys transplanted into large recipients and lower than anticipated in large kidneys transplanted into small donors.[6,38] This observation is supported by others who showed that the donor kidney adapts to the recipient's body size and that a higher recipient body mass index is associated with a higher GFR in the shorter term.[15,16,36,39] Importantly, higher GFRs in recipients with higher body mass index were accompanied by higher filtration fractions, suggesting hyperfiltration.[39] Healthy, single kidneys may maintain high filtration without signs of significant damage over the long term.[12] In less healthy kidneys, however, a high metabolic burden and consequent hyperfiltration may lead to progressive deterioration in kidney function.[2,6,40,41]

Our choice of the CG eGFR formula may be considered a weakness because the CKD-EPI formula performs better in subjects with native kidneys.[19] In addition, the CG formula estimates creatinine clearance and not GFR, and may introduce bias in overestimation of GFR at the lower levels of renal function. In transplantation, however, the superiority of one formula over another has not been proven, and with GFRs > 45 mL/min per 1.73m^2, which includes most stable transplant patients, the CG-GFR performs well.[42,43] We therefore selected the CG-GFR, also to build on Sberro's previous work. Future studies should evaluate cystatin C-based prediction formulae which may be superior.[44] The consistency of our findings of the AI-GFR in the LDs, based solely on eGFRs, does support our use of eGFRs for comparisons within and between donor groups. Utilization of the LoObsSCr in year 1 as a reference against which to determine accuracy of the ExpSCr is an inherent weakness in our and other similar studies, given that a single low SCr may be an outlier for a specific patient. At present, however, the LoObsSCr is the closest reflection of a kidney's best possible function. After year 1, however, we used ObSCr values at each time point, avoiding this potential limitation. Another important limitation is the use of surrogate markers for metabolic demand and nephron supply in the eGFR calculations. Direct measurements of energy expenditure or nephron number are not routinely available; therefore; we used alternative widely accepted markers.[21,37,45] Changes in posttransplant weight and percent lean body mass may impact recipient metabolic demand and SCr values and therefore may have affected the accuracy of the eGFR and creatinine calculations.

TABLE 2.

Posttransplant kidney function assessed by different approaches

Time point	d 7 (79/67)	mo 3 (78/65)	y 1 (78/66)	y 3 (75/59)	y 4 (73/56)	y 5 (68/52)
			ObsSCr, μmol/L			
LD	144 ± 79	132 ± 31	127 ± 37	120 ± 28	122 ± 34	125 ± 29
DD	235 ± 123	135 ± 70	120 ± 42	118 ± 36	126 ± 52	117 ± 51
P	0.0003	0.79	0.30	0.75	0.66	0.45
			CG eGFR, mL/min			
LD	68 ± 23	69 ± 22	72 ± 25	76 ± 27	73 ± 30	74 ± 16
DD	51 ± 25	66 ± 22	71 ± 23	72 ± 25	69 ± 27	75 ± 12
P	<0.0001	0.45	0.7	0.38	0.42	0.87
			ExpSCr-ObsSCr, %			
LD	−27 ± 63	−20 ± 42	−14 ± 41	−9 ± 38	−11 ± 41	−12 ± 33
DD	−168 ± 228	−54 ± 78	−41 ± 67	−36 ± 57	−47 ± 86	−38 ± 56
P	0.0001	0.0014	0.004	0.0015	0.002	0.0021

These factors likely contribute to the recognized underperformance of GFR calculations in the transplant population in general and are very difficult to control for in the clinical setting.[42] Subgroup analysis would have been ideal to validate the clinical utility of our formula given all the caveats; however, in this preliminary study, we elected not to preselect cases, regardless of clinical events or extremes of age or weight because of the small numbers.

The true utility of our ExpSCr versus ObsScr approach cannot be determined from our cohort, as despite the generally lower than expected renal function in our DDs compared to LDs, both groups showed stable transplant function and excellent graft and patient survival rates over 5 years of follow-up. The relatively short follow-up is therefore a limitation, and it is possible, as with other cohorts, true differences in outcome may become apparent with time, which will assist in better understanding of the impact of this approach.[2,46]

Assessment of organ function must reflect the uniqueness of transplantation—the adaptation of an organ developed to meet the donor's requirements subsequently introduced into a setting of a different metabolic demand. Despite the limitations discussed, we suggest that the proposed formula is the most physiologically relevant current method to estimate expected renal function after transplantation. Heightened awareness that an individual kidney may not be functioning at its best possible "baseline" level is clinically important and should prompt thought and investigation as to why this discrepancy is present and potentially permit early intervention to improve renal function and thereby optimize long-term transplant function.

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